Optimal Sedation in Ventilated Patients with Sepsis and Septic Shock

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KEYWORDS

• Sepsis • Septic shock • Sedation • Delirium

KEY POINTS

- Metabolism of sedative medications is altered during sepsis.
- The *A*ssess, Prevent, and Manage Pain, *B*oth Spontaneous Awakening Trials and Spontaneous Breathing Trials, *C*hoice of analgesia and sedation, *D*elirium: Assess, Prevent, and Manage, *E*arly mobility and Exercise, and *F*amily engagement and empowerment bundle should be used as a basic framework for sedation.
- A analgesia-first or analgosedation approach should be used before adding additional sedative medications.

INTRODUCTION

Sedation and analgesia are cornerstones of care for critically ill patients requiring mechanical ventilation in the intensive care unit (ICU).[1] These interventions aim to alleviate pain, reduce stress, and promote tolerance to invasive procedures, ultimately enhancing patient outcomes.[1] Proper sedation practices are crucial for ensuring patient comfort, safety, and the overall effectiveness of treatment. However, sedation must be carefully balanced to avoid complications associated with over-sedation or under-sedation, making it a critical area of focus for ICU clinicians.

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Abbreviations	
ABCDEF (A2F)	*A*ssess, Prevent, and Manage Pain, *B*oth Spontaneous Awakening Trials and Spontaneous Breathing Trials, *C*hoice of analgesia and sedation, *D*elirium: Assess, Prevent, and Manage, *E*arly mobility and Exercise, and *F*amily engagement and empowerment
ARDS	acute respiratory distress syndrome
COVID-19	coronavirus disease 2019
ICU	intensive care unit
IL	interleukins
MENDS-2	maximizing the efficacy of sedation and reducing neurologic dysfunction and mortality in sepsis
NONSEDA	no sedation or light sedation in critically ill, mechanically ventilated patients
PADIS	prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU
PRIS	propofol-related infusion syndrome
PTSD	depression and posttraumatic stress disorder
RASS	Richmond Agitation-Sedation Scale
SPICE 3	sedation practice in intensive care evaluation
TNF	tumor necrosis factor

ANALGESIA AND SEDATION IN THE CRITICALLY ILL: NEED AND POTENTIAL SIDE-EFFECTS

Critically ill patients often experience significant pain and stress due to their underlying medical conditions, bed rest, invasive devices, and therapeutic interventions.[2,3] Accordingly, it is critical for clinicians to direct initial attention toward analgesia when considering *sedation* in the mechanically ventilated patient. Simply having an endotracheal tube in the trachea causes discomfort in many patients. A proactive approach to managing pain has been strongly recommended by the most recent Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU (PADIS).[4] Recognition of the presence of pain is often difficult since many mechanically ventilated patients are unable to convey its presence and clinical variables such as changes in vital signs are often not reliable indicators. Therefore, a high level of vigilance toward analgesia is essential and use of pain scales recommended.[4] Pain may cause many adverse effects including increased endogenous catecholamine activity, myocardial ischemia, hypercoagulability, hypermetabolic states, sleep deprivation, anxiety, and delirium[5,6]; so treating pain has been shown to ameliorate some of these effects.[7]

Sedation requirements can vary significantly among mechanically ventilated patients. Although nonpharmacologic strategies, such as ensuring comfortable positioning and providing verbal reassurance, are appropriate initial approaches, pharmacologic agents are sometimes required. There are numerous indications for administering sedatives to ICU patients on mechanical ventilation. Anxiety in patients undergoing mechanical ventilation can arise from various factors, including uncertainty regarding surroundings or condition, uncomfortable experiences and/or anticipation of such, and isolation from others. Sedatives may be necessary to facilitate nursing care, since procedures such as endotracheal suctioning, dressing changes, and repositioning often result in distress that goes beyond the experience of pain.[1] Many patients requiring mechanical ventilation suffer from cardiopulmonary instability and impaired gas exchange. Sedatives and analgesics have been shown to reduce oxygen consumption and autonomic hyperactivity.[8] Amnesia is often cited as a rationale for sedating mechanically ventilated patients; however, its significance during

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critical illness remains uncertain. Notably, complete amnesia over prolonged periods of mechanical ventilation in the ICU has not been shown to provide any clear benefit. On the contrary, some evidence indicates that extended ICU-related amnesia may negatively impact long-term neuropsychiatric recovery from critical illness.[9–11] Conditions such as depression and posttraumatic stress disorder (PTSD) are among the long-term consequences of recovery in critically ill patients.[12,13] Additionally, studies suggest that reduced awareness due to sedation or the underlying illness itself may contribute to the development of PTSD, while preserving awareness during mechanical ventilation could potentially mitigate this risk.[9,10] With increasing attention to long-term recovery from critical illness,[12,14–16] a better understanding of the relationship between sedation and recovery should be forthcoming. It is indisputable however, that complete amnesia is mandatory whenever neuromuscular blocking agents are administered. Delirium has been reported in over 60% to 80% of mechanically ventilated patients with most of the cases occurring in the ICU with an average time of onset between the second and the third day.[17,18] Evidence shows that delirium is a strong predictor of increased length of mechanical ventilation, longer ICU stays, increased cost, long-term cognitive impairment, and mortality.[18–22] Data showed a clear association between decreased exposure to sedatives, particularly benzodiazepines, and improved patient outcome especially in terms of delirium incidence.[23,24]

Over the last 2 decades sedation paradigms in general have embraced targeted (with the use of sedation scales) and light levels of sedation, the incorporation of daily and coordinated awakening and breathing trials,[22,25,26] and the move away from benzodiazepine-based sedation toward use of analgosedation practices or then propofol-or-dexmedetomidine-based sedation regimens.[4] Yet, these established practices have been questioned in patients with severe acute respiratory distress syndrome (ARDS) and those with septic shock, made even more evident during the coronavirus disease 2019 (COVID-19) pandemic, when established sedation practices were often abandoned.[27,28] Unique characteristics of patients with septic shock (and often associated ARDS) therefore need to be explored to determine best sedation practices for this subset of critically ill patients and critically evaluate the literature to determine if truly this population is different and requiring alternative approaches to sedation in the ICU.

SPECIAL CONSIDERATIONS OF SEDATIVE MEDICATION IN SEPSIS AND SEPTIC SHOCK

Patients with sepsis and septic shock experience varying degrees of organ dysfunction, altered drug metabolism, hemodynamic instability, increased vascular permeability, and impaired tissue perfusion.[29] The aberrant physiology observed in these patients presents significant challenges to achieving optimal sedation for mechanical ventilation and requires consideration of the pharmacokinetics unique to this critically ill population.[2] Furthermore, the risks associated with sedative medication use, including unnecessarily prolonging mechanical ventilation, contributing to the development of delirium, and delaying recovery from critical illness, must be considered when determining the sedation strategy for each critically ill patient.[30,31]

Pharmacokinetics Unique to Sepsis and Septic Shock

Metabolism

Reduced hepatic blood flow, altered enzyme expression, and changes in drug-protein interactions contribute to decreased metabolism of sedative drugs in septic shock. Hepatic clearance is contingent upon blood flow through the liver and the hepatic

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extraction ratio for a given drug, the proportion of drugs removed from each pass through the liver.[30] Drugs with high extraction ratios, such as midazolam, fentanyl, and propofol, are primarily dependent on hepatic blood flow and less sensitive to changes in liver function. In contrast, drugs with low extraction ratio are less dependent on blood flow and more affected by impaired hepatic function.[29] Dexmedetomidine is considered an intermediate extraction ratio drug as its metabolism is contingent upon both hepatic blood flow and function.[32]

The shock state and the α-adrenergic receptor stimulating agents used to treat it, such as norepinephrine, contribute to reduced hepatic blood flow, thereby altering the hepatic metabolism of high extraction ratio drugs.[29] Increased intrathoracic pressure resulting from mechanical ventilation may contribute to hepatic congestion, further decreasing the metabolism of high extraction ratio drugs.[33] However, there is a paucity of studies focused specifically on the metabolism of sedatives in mechanically ventilated septic patients with reduced hepatic blood flow.

Sepsis involves a dysregulated host immune response to infection.[34] Inflammation has been shown to decrease drug metabolism via downregulation of multiple cytochrome systems and drug transporters.[35,36] Decreased hepatic perfusion in shock can cause ischemic injury, and the use of hepatotoxic drugs necessary for the treatment of the patient in shock, as well as the release of endotoxin and other pathogen-derived toxins, can directly injure hepatocytes, further impairing the metabolic function of the liver in sepsis.[30,35,36] Moreover, concomitant use of cytochrome-inhibiting medications can compound the impaired ability to metabolize low and intermediate-extraction ratio drugs (**Table 1**).[29]

Distribution

The volume of distribution of sedatives is altered in sepsis. Causes of this include increased vascular permeability, resulting in the third spacing of fluids, and increased total body water following fluid resuscitation, which can contribute to increased volume of distribution of sedatives. Alternatively, decreased volume of distribution may result from reduced peripheral blood flow due to both endogenous and exogenous catecholamines and suppressed cardiac output.[29] Furthermore, continuous renal replacement therapy and extracorporeal membrane oxygenation can lower the concentration of a given drug by increasing the volume of distribution and via circuit sequestration.[30]

The protein binding of drugs is altered in sepsis. Hypoalbuminemia is commonly observed in sepsis and can result in an increased free fraction and altered metabolism.[30,32] For example, propofol exhibits high albumin binding, with approximately 98% bound in nonseptic patients; hypoalbuminemia has been linked to increased adverse cardiovascular effects, such as hypotension, due to elevated free propofol plasma concentration.[37] Increased free fraction and volume of distribution resulting from hypoalbuminemia also contribute to delayed clearance of midazolam and dexmedetomidine.[29,32] The acute phase reactant α1-acid glycoprotein (AAG) may limit the extent to which hypoalbuminemia increases the free fraction of highly protein-bound drugs, as many drugs, including propofol and fentanyl, readily bind AAG.[29]

Excretion and Absorption

Excretion and absorption are of lesser concern when considering the pharmacokinetics of sedatives used in mechanically ventilated patients. Although the presence of shock and the use of pressors may reduce gastrointestinal (GI) absorption of medications administered orally, intravenous infusions of sedatives have 100% bioavailability.[29] In addition, renal failure is common in mechanically ventilated patients with sepsis.

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Table 1
Pharmacokinetics of commonly used sedatives in mechanically ventilated patients

	Propofol	Dexmedetomidine	Fentanyl	Midazolam
Volume of distribution	2–10 L/kg	0.8–1.5 L/kg	3–8 L/kg	1–3 L/kg
Percent protein bound	97%–99%	~94%	79%–87%	95%–98%
Extraction ratio	High (>0.7, flow-limited)	Intermediate (~0.5–0.7)	High (>0.7, flow-limited)	High (>0.7, flow-limited)
Hepatic clearance Rate	~1.5–2 L/min	~0.65–0.75 L/min	~0.5–1.5 L/min	~0.5–1.2 L/min
Renal clearance	<0.3%	<1% (metabolites: ~95% excreted)	<10%	<1% (metabolites: ~90% excreted)
Half-life	1–3 h (context-sensitive half-life longer)	2–3 h	2–4 h (context-sensitive half-life longer)	1.5–3 h (context-sensitive half-life longer)
Primary excretion	Urine (~88%), feces (~2%)	Urine (~95%), feces (~4%)	Urine (~75%), feces (~10%)	Urine (~90%), feces (~10%)
Metabolism site	Liver (CYP2B6, CYP2C9, glucuronidation)	Liver (glucuronidation, minor CYP2A6 involvement)	Liver (CYP3A4)	Liver (CYP3A4/5)
Active metabolites	None	None	None	Yes (1-hydroxymidazolam)
Key clinical notes	Rapid onset and clearance; prolonged context-sensitive half-life; lipophilic; rarely affected by organ dysfunction	Highly predictable kinetics; dose adjustments in liver impairment; relatively short context-sensitive half-life	Highly lipophilic; accumulation in fat during prolonged use; clearance reduced in liver dysfunction	Prolonged effects with liver disease or CYP3A4 inhibitors; lipophilic

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However, dexmedetomidine, fentanyl, and propofol are hepatically metabolized to inactive compounds with clinically insignificant pharmacologic effects; only midazolam has an active metabolite that must be considered in renal failure.[37,38] Accumulation of midazolam's metabolite, 1-hydroxymidazolam, can contribute to prolonged sedation in renal failure.[39] Although midazolam is not cleared through renal replacement therapy, its glucuronidated metabolite 1-hydroxymidazolam is cleared effectively.[40]

In practice, sedative medications should be titrated to effect using a validated sedation scale (eg, the Richmond Agitation-Sedation Scale, or RAAS) targeting the least effective degree of sedation (most commonly light sedation with RASS of −2) with daily interruptions of sedation to assess readiness for extubation. However, as the pathophysiologic changes that occur in sepsis and their effect on sedative distribution, metabolism, and excretion are complex and incompletely understood, knowledge of the pharmacokinetic principles is necessary to avoid harm, reduce complications, and care for this critically ill patient population effectively.

Pharmacokinetic and Pharmacodynamic Considerations of Commonly Used Sedative Agents in Sepsis and Shock

Sedative selection for critically ill, mechanically ventilated patients with sepsis and shock requires an understanding of the interaction between patient-specific factors, the underlying condition necessitating ICU admission, and the pharmacologic profiles of each drug. The choice of sedative should attempt to balance the benefits of effective sedation against the risks of sedation-associated adverse outcomes. The following section offers an overview of the 4 most used sedatives in the ICU, emphasizing pharmacologic properties, clinical applications, and associated risks. Understanding the advantages and limitations of each drug is critical to optimizing sedation strategies to improve outcomes, minimize complications, and ensure optimal patient care.

Midazolam

The most used benzodiazepine sedative in the ICU is midazolam. Midazolam is lipophilic, allowing it to readily cross the blood-brain barrier, contributing to the rapid onset of sedation.[41] However, this drug accumulates in adipose tissue, which can result in delayed metabolism and prolonged sedation. The sedative effects of midazolam can linger for days, confounding attempts at neurologic assessment and weaning of sedation, thereby prolonging mechanical ventilation.[38] Recent trials have demonstrated that benzodiazepines are associated with increased incidence of delirium,[42] prolonged intubation,[43] and longer ICU lengths of stay[44] relative to nonbenzodiazepine sedative medications. Nonetheless, benzodiazepines may still have a role in sedating patients at risk of alcohol or benzodiazepine withdrawal and in those patients at risk of seizure.[41]

Fentanyl

In accordance with the analgesia-first approach to sedation, opioid use enables multimodal analgosedation strategies that allow patients to tolerate the lightest possible level of sedation, minimizing net sedative drug exposure. As renal failure is common in mechanically ventilated patients with sepsis and shock, neither morphine nor hydromorphone are preferred agents due to the risk of active metabolite or parent drug accumulation, respectively.[41] The synthetic opioids fentanyl and, less commonly, remifentanil serve as the foundation of ICU analgosedation. Like midazolam, fentanyl is a lipophilic drug with a rapid onset of action and the propensity to accumulate in adipose tissue, potentially leading to prolonged sedation.[37] The adverse effects of opioid use are known and include tolerance,[45] withdrawal,[46] and respiratory depression.[47] Moreover, opioid exposure has been demonstrated to increase the risk of delirium in a dose-dependent manner.[48]

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Propofol

Propofol is another lipophilic sedative that readily crosses the blood-brain barrier, leading to the rapid onset of sedation; however, discontinuing propofol results in faster recovery of consciousness relative to benzodiazepine sedatives.[41] Additionally, the use of propofol is associated with decreased in-hospital mortality, shorter ICU lengths of stay, and earlier discontinuation of mechanical ventilation relative to sedation with benzodiazepines.[49] Considering propofol's large volume of distribution and lipophilicity, extended infusions can cause prolonged sedation.[37] Additional adverse consequences of propofol use include hypotension, hypertriglyceridemia, and the rare occurrence of propofol-related infusion syndrome. Regarding propofol-induced hypotension, this known phenomenon occurs as a result of decreased vascular tone.[50] Transitioning from propofol to dexmedetomidine has been shown to ameliorate this effect, as evidenced by reduced norepinephrine requirements in patients with septic shock.[51] Hypertriglyceridemia occurs as a result of propofol's lipid emulsion formulation. Use of this sedative necessitates regular monitoring of triglyceride levels and consideration of caloric intake secondary to propofol when developing a nutrition plan in patients with sepsis and shock. Although more common in pediatric patients, prolonged infusions of propofol require monitoring for propofol-related infusion syndrome (PRIS). PRIS occurs when free fatty acids from propofol's lipid emulsion accumulate in the setting of inadequate beta-oxidation and insufficient carbohydrate availability, causing a potentially fatal reduction in cellular respiration.[52] Symptoms of PRIS include heart failure, bradycardia, rhabdomyolysis, and metabolic acidosis.[37] The use of pressors, steroids, as well as high doses (>4 mg/kg/hour) over prolonged periods (>48 hours) increases the risk.[52] Creatinine kinase should be monitored if prolonged propofol infusions are required.[53]

Dexmedetomidine

Dexmedetomidine is an alpha-2 adrenergic agonist that inhibits the sympathetic nervous system, resulting in both sedation and analgesia. Because of its sympatholytic effects, lower doses may result in hypotension due to reduced catecholamine levels and increased vagal tone. Conversely, higher doses may produce hypertension because of the stimulation of vascular smooth muscle alpha-2 receptors and the resulting baroreflex-mediated bradycardia.[32] This biphasic response is most pronounced in elderly patients and is typically observed when infusion rates exceed 0.7 μg/kg/h.[37] The unique mechanism of action of dexmedetomidine enables lighter sedation levels, allowing patients to be easily arousable and induces a sedative state that resembles natural sleep.[32] Furthermore, this drug leads to less respiratory depression compared to other sedatives and reduces myocardial oxygen demand.[41] Interestingly, dexmedetomidine also appears to up-regulate the expression of alpha-1 receptors, thereby increasing sensitivity to vasopressors,[51] and has been shown to augment the inflammatory response in sepsis.[54] The clinical relevance of the immunomodulatory effect of dexmedetomidine is still under investigation.[55] Dexmedetomidine use is contraindicated in those patients with bradycardia, and its use should be discontinued if second or third-degree heart block develops.[37] Caution should be exercised when using this sedative in patients with ischemic stroke due to possible reduction in cerebral perfusion pressure.[37] Relative to benzodiazepine sedatives, dexmedetomidine is associated with a decreased risk of delirium and shorter durations of both mechanical ventilation and ICU lengths of stay.[56,57] In mechanically ventilated patients with sepsis, a comparison of dexmedetomidine and propofol has demonstrated equivocal outcomes regarding delirium and ventilator-free days, 90-day mortality, and global cognition at 6 months, as will be discussed later.[55]

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Immunomodulatory Properties of Sedative Medication in Sepsis and Septic Shock

To understand how sedation may play a role in dysregulating the body's natural response to inflammation, we need to first succinctly review the inflammatory response to infection. Sepsis is the systemic inflammatory response to infection and is characterized by dysregulated production of cytokines, producing a pathologic state that causes tissue injury, organ dysfunction, and death.[58,59] It is characterized by an early unrestrained production of *pro-inflammatory cytokines*, including tumor necrosis factor (TNF), interleukins (IL) such as IL-1 and IL-6, and late mediators such as high-mobility group protein B1, all of which perpetuate the inflammatory response and lead to organ dysfunctions.[58,59] *Anti-inflammatory* cytokines such as soluble TNF receptor-1, IL-1ra, and IL-10 are released in an attempt to attenuate the proinflammatory response and reduce organ damage; failure or dysregulation of this compensatory anti-inflammatory response syndrome further worsens outcomes.[58,59] The brain also responds to systemic infections and injury with an inflammatory response of its own that includes the production of cytokines, cell infiltration, and tissue damage.[60,61] This local inflammatory response is thought to alter patterns of neuronal activity, resulting in brain organ dysfunction (delirium and/or coma). In addition, the parasympathetic (cholinergic) anti-inflammatory pathway plays an important role in attenuation of proinflammatory cytokines from macrophages, without any effects on antiinflammatory cytokines such as IL-10.[62,63] The body generally regulates this balance between the proinflammatory and anti-inflammatory cytokines; unfortunately, commonly prescribed sedative agents may alter the endogenous balance and contribute to worse outcomes.

GABA-ergic agents (eg midazolam) impair nuclear factor kappa B and mitogen activated protein kinase signaling, leading to reduced responsiveness to inflammatory stimuli, including pathogens.[64,65] This effect is typically manifested as reduced cytokine production and may have utility in septic shock; however, this mechanism also blunts bacterial killing.[64,65] *In vivo* animal studies, for example, have demonstrated that the GABA-ergic agents increase mortality in live bacterial infection that may be caused by impairment of neutrophil and macrophage function.[64,66] Review of the available evidence suggests that this impaired immune response to pathogens is a cross-class effect of GABA agonists studied.[64] Consistent with the hypothesis that GABA-ergic agents may impair immune responses to infection, critically ill patients sedated with midazolam appear more susceptible to secondary bacterial infections than those sedated with the alpha$_2$ agonist dexmedetomidine, and septic patients on lorazepam have a greater likelihood of death than patients sedated with dexmedetomidine.[42,67]

Propofol and dexmedetomidine are routinely recommended for sedation in critically ill patients, many with septic shock, yet may differentially affect inflammation and clinical outcomes in sepsis. It is well known that dysregulated production of proinflammatory cytokines is associated with worse outcomes in sepsis.[58] The body itself attempts to reign-in this proinflammatory cytokine cascade by 2 mechanisms—*(a)* the production of anti-inflammatory cytokines and *(b)* the parasympathetic (cholinergic) reflex that attenuates inflammation.[58,63] Propofol shows favorable properties by reducing proinflammatory cytokines in animal models; however, human studies have been contradictory with an increase in proinflammatory cytokine production.[68–70] Additionally, propofol has not been shown to have any effect on the parasympathetic reflex. Dexmedetomidine, on the other hand, has consistently attenuated proinflammatory cytokines in animal and human studies, with improvements in outcomes including survival, and its vagomimetic action may play a role in potentiating the cholinergic-mediated anti-inflammatory reflex.[64,71]

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Taken together, important differences exist in the immunomodulatory properties of available sedative medications, yet it is unclear whether these have impact on patient outcomes, or on certain subgroups, when best state of the art practices are employed.

EVIDENCE-BASED GUIDELINES FOR USE OF SEDATIVE MEDICATION IN PATIENTS WITH SEPSIS AND SEPTIC SHOCK

Once the indications for sedation are established, a goal-directed approach to the delivery of psychoactive medications needs to be employed to avoid oversedation, and to promote earlier extubation. The Society of Critical Care Medicine (SCCM) PADIS guidelines recommend the use of the RASS and the Riker Sedation-Agitation Scale as 2 reliable and valid tools with the best psychometric properties.[4,72] Several electroencephalogram-based instruments for assessing level of sedation are now available[73,74] and are in the process of undergoing rigorous reliability and validity testing and may become available for routine use in the near future. Sedation strategies for critically ill patients receiving mechanical ventilation have radically evolved over the past 20 years. The Clinical Practice Guidelines from the Society of Critical Care Medicine of 2002, 2013, and 2018 witnessed a major transition from sustained sedation to an analgesia-first and light sedation paradigm to recommendations to avoid benzodiazepines in favor of propofol and dexmedetomidine.[4,72,75] Paradigm shifting trials led to the adoption of practices such as daily sedative interruption, light sedation, analgesia first, and early mobilization.[25,76–78]

An analgesia-first approach is recommended, with pain management prioritized before sedation initiation, as untreated pain exacerbates agitation and distress.[72] Multimodal analgesia, may play an important role in achieving clinically appropriate goals in critically ill patients,[79] while reducing the need for opioids and sedation. When sedation is required to account for significant anxiety, agitation, and ventilator-patient dyssynchrony, the recent 2018 PADIS guidelines recommended targeting the lightest level of sedation and performing coordinated daily awakening and breathing trials.[4] These guidelines suggested using propofol in cardiac patients and either propofol or dexmedetomidine in medical or noncardiac surgical patients.[4] Following the PADIS release, studies such as the Sedation Practice in Intensive Care Evaluation (SPICE 3)[80] and Maximizing the Efficacy of Sedation and Reducing Neurologic Dysfunction and Mortality in Sepsis (MENDS-2)[55] have been published showing no difference in dexmedetomidine versus usual care (SPICE III) or propofol (MENDS2) in clinical outcomes. Importantly, MENDS-2 enrolled patients with sepsis and shock and found that when light sedation was targeted, the choice of the sedative medication (propofol or dexmedetomidine), did not impact acute and long-term patient outcomes, and did not result in significant differences in adverse events such as hypotension. Furthermore, the No Sedation or Light Sedation in Critically Ill, Mechanically Ventilated Patients (NONSEDA) trial, which compared no sedation versus light sedation, found no significant impact on 90-day mortality or ICU/ventilator-free days.[81] In all 3 studies (SPICE III, MENDS2, and NONSEDA), the median APACHE score were greater than 20, reflecting moderate to severe illness, with most patients on mechanical ventilation and in shock; yet, targeting light levels of sedation was shown to be safe, with no differences between propofol and dexmedetomidine when such a technique was employed. There were no significant differences in individual organ dysfunctions.[55] Follow-up studies evaluating heterogenicity of treatment effect have suggested that dexmedetomidine may be associated with worse

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outcomes in younger patients as compared to propofol, yet the biological plausibility is unclear and this needs to be investigated in a larger study before specific recommendations can be made.[82]

The COVID-19 pandemic introduced a range of new challenges and realities in providing sedation to hundreds of thousands of patients on mechanical ventilation due to manpower, drug shortages, the severe pneumonia and hypoxemia patients experienced[83,84] and questioned the evidence outlined thus far that had been built over 2 decades of rigorously conducted trials. Early reports described unique ARDS characteristics imploring the use of deep sedation.[85] The practice change was quantified in the COVID-D multicenter cohort study that included 69 adult ICUs, across 14 countries and enrolled over 2000 patients.[27] Data showed that 64% and 71% of patients received benzodiazepines and propofol for a median of 7 days respectively,[27] and that the use of benzodiazepine medications was independently associated with delirium. A significant proportion of mechanically ventilated patients spent close to a week deeply sedated.[27] While it is true that a small subset of patients with severe ARDS and septic shock may have significant ventilator dyssynchrony, choosing the best ventilator setting should be prioritized over increasing sedation.[86] Once that is optimized, early deep sedation with neuromuscular blockade may be considered, though this there are conflicting data about the benefits of early neuromuscular blockade in patients with severe ARDS.[87,88] This underscores the fact that for the vast majority of patients with ARDS (including those with COVID ARDS) and sepsis/septic shock, the recommended PADIS guidelines should serve as the framework for managing sedation.[28] A pragmatic approach to implement the guidelines is the *A*ssess, Prevent, and Manage Pain, *B*oth Spontaneous Awakening Trials and Spontaneous Breathing Trials, *C*hoice of analgesia and sedation, *D*elirium: Assess, Prevent, and Manage, *E*arly mobility and Exercise, and *F*amily engagement and empowerment (ABCDEF [A2F]) bundle, which represents an evidence-based guide for clinicians to approach the organizational changes needed for optimizing ICU patient recovery and outcomes, including for those with sepsis and shock. The tenets of the A2F bundle are: *A*ssess, Prevent, and Manage Pain, *B*oth Spontaneous Awakening Trials and Spontaneous Breathing Trials , *C*hoice of analgesia and sedation, *D*elirium: Assess, Prevent, and Manage, *E*arly mobility and Exercise, and *F*amily engagement and empowerment. This A2F Bundle has been tested in over 15,000 patients and has been shown to be associated with improved patient outcomes.[89,90]

SUMMARY

In most patients with sepsis and septic shock on mechanical ventilation, it is recommended that health care providers use and analgesia-first approach and target light levels of sedation, if required. If a sedative is required, propofol or dexmedetomidine should be used, factoring in patient characteristics including organ dysfunctions, and sedation scales should be used to objectively target desired level of sedation. The A2F bundle should be employed, paying attention to daily sedation interruptions to ensure that sedatives are used for the shortest time to liberate patients from mechanical ventilation. In rare situations with severe ARDS or hemodynamic perturbation in an agitated patient, sedation strategies should be tailored to that specific patient, without abandoning best practice guidelines for other patients.[91] There is a growing need to advance sedation practices through well-designed clinical trials that focus on population-specific sedation strategies and the evaluation of newer sedatives, with the goal of improving patient-centered outcomes.

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CLINICS CARE POINTS

- Prioritize analgesia before sedation in mechanically ventilated patients with sepsis and septic shock to reduce sympathetic activation, improve comfort, and avoid excess sedative use.
- Use validated sedation scales (eg, Richmond Agitation-Sedation Scale) to target light levels of sedation (RASS –2 to 0), unless deep sedation is specifically indicated (eg, neuromuscular blockade, severe ARDS with ventilator dyssynchrony).
- Avoid benzodiazepines whenever possible due to their association with prolonged mechanical ventilation, increased risk of delirium, and adverse long-term neurocognitive outcomes.
- Dexmedetomidine offers potential benefits in sepsis due to its minimal respiratory depression, possible upregulation of vasopressor sensitivity, and immunomodulatory effects via the cholinergic anti-inflammatory pathway.
- Monitor for adverse effects of prolonged sedation: Target early liberation from mechanical ventilation through coordinated daily sedation interruption and spontaneous breathing trials, following the ABCDEF (A2F) bundle framework.
- COVID-19 and severe ARDS may necessitate deeper sedation, but clinicians should reassess frequently and return to evidence-based sedation targets as soon as feasible.
- Pharmacokinetic changes in septic shock—including altered hepatic blood flow, protein binding, and distribution—require individualized sedative dosing to prevent accumulation and toxicity.

DISCLOSURES

The authors do not have any conflicts of interest or disclosures.

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